ABSTRACT ~ Background: The short-term safety profile of once-daily valbenazine (NBI-98854) has been evaluated in several double-blind, placebo-controlled (DBPC) trials in adults with tardive dyskinesia (TD) who had a diagnosis of schizophrenia/schizoaffective (SCHZ) disorder or mood disorder. Studies with longer treatment duration (up to 48 weeks) were conducted to evaluate the long-term safety of this novel drug in subjects with TD. Methods: The pooled long-term exposure (LTE) population included valbenazine-treated subjects from 3 studies: KINECT (NCT01688037: 6-week DBPC, 6-week open-label; KINECT 3 (NCT02274558: 6-week DBPC, 42-week blinded extension, 4-week drug-free follow-up); KINECT 4 (NCT02405091: 48-week open-label, 4-week drug-free follow-up). Safety assessments included adverse events (AEs), laboratory tests, vital signs, electrocardiograms (ECGs), and extrapyramidal symptom (EPS) scales. Psychiatric stability was monitored using the Positive and Negative Syndrome Scale (PANSS) and Calgary Depression Scale for Schizophrenia (CDSS) (SCHZ subgroup), as well as the Montgomery-Åsberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS) (mood subgroup). All data were analyzed descriptively. Results: The LTE population included 430 subjects (KINECT, n = 46; KINECT 3, n = 220; KINECT 4, n = 164), 71.7% with SCHZ and 28.3% with a mood disorder; 85.5% were taking an antipsychotic (atypical only, 69.8%; typical only or typical + atypical, 15.7%). In the LTE population, treatment-emergent AEs (TEAEs) and discontinuations due to AEs were reported in 66.5% and 14.7% of subjects, respectively. The TEAE incidence was lower in the SCHZ subgroup (64.4%) than in the mood subgroup (71.9%). The 3 most...
common TEAEs in the SCHZ subgroup were urinary tract infection (UTI, 6.1%), headache (5.8%), and somnolence (5.2%). The 3 most common TEAEs in the mood subgroup were headache (12.4%), UTI (10.7%), and somnolence (9.1%). Mean score changes from baseline to end of treatment (Week 48) indicated that psychiatric stability was maintained in the SCHZ subgroup (PANSS Total, −3.4; PANSS Positive, −1.1; PANSS Negative, −0.1; PANSS General Psychopathology, −2.2; CDSS total, −0.4) and the mood subgroup (MADRS Total, 0.0; YMRS Total, −1.2). These scores remained generally stable during the 4-week drug-free follow-up periods.

In the LTE population, mean changes in laboratory parameters, vital signs, ECG, and EPS scales were generally minimal and not clinically significant.

Conclusion: Valbenazine appeared to be well tolerated in adults with TD who received up to 48 weeks of treatment. In addition to long-term efficacy results (presented separately), these results suggest that valbenazine may be appropriate for the long-term management of TD regardless of underlying psychiatric diagnosis (SCHZ disorder or mood disorder).


INTRODUCTION

- Tardive dyskinesia (TD) is an involuntary, often irreversible movement disorder that can result from exposure to dopamine receptor blocking agents (DRBAs), including antipsychotics.
- Inhibition of vesicular monoamine transporter 2 (VMAT2) can modulate dopaminergic neurotransmission by reducing synaptic dopamine levels, thereby improving TD symptoms.
- Valbenazine (INGREZZA) is a novel, highly selective VMAT2 inhibitor that is the first and only FDA-approved product indicated for the treatment of TD in adults.
- This pooled, post-hoc analysis evaluated the long-term safety of valbenazine in participants with TD and a diagnosis of either schizophrenia/schizoaffective disorder or mood disorder.

METHODS

Study Design

- The pooled long-term exposure (LTE) population included valbenazine-treated participants from 3 studies (Figure 1).
- Analyses of KINECT and KINECT 3 data are final; analyses of KINECT 4 data are interim.
  - The pooled LTE 80 mg group included participants who received once-daily valbenazine 80 mg in KINECT 3 or KINECT 4.
  - The pooled LTE 40 mg group included participants who received once-daily valbenazine 40 mg in KINECT 3 or KINECT 4, along
with participants who received valbenazine 50 mg in KINECT (including participants who initially received 2 weeks of valbenazine 100 mg)

Participants

- Key inclusion criteria
  - *Diagnostic and Statistical Manual of Mental Disorders* (e.g., DSM-IV) diagnosis of DRBA-induced TD for $\geq 3$ months prior to screening
  - DSM diagnosis of schizophrenia, schizoaffective disorder, or mood disorder; stable psychiatric status (Brief Psychiatric Rating Scale score $< 50$ at screening)
  - Moderate or severe TD as qualitatively assessed by a blinded, external reviewer using an Abnormal Involuntary Movement Scale (AIMS) video conducted at screening

- Key exclusion criteria
  - Active, clinically significant, and unstable medical conditions within 1 month prior to screening
  - Comorbid movement disorder (e.g., parkinsonism, akathisia, truncal dystonia) that was more prominent than TD
  - Significant risk for active suicidal ideation, suicidal behavior, or violent behavior
  - Stable doses of concomitant medications to treat the psychiatric disorders were permitted throughout the studies
Long-Term Safety and Tolerability of Valbenazine (NBI-98854) in Subjects

Analyses

- Populations
  - Overall LTE safety population: all participants who received ≥1 dose of assigned study treatment
  - Diagnostic subgroups: participants with schizophrenia/schizoaffective disorder or mood disorder
- Assesments: adverse events (AEs), laboratory tests, vital signs, and electrocardiograms (ECGs)
- Extrapyramidal symptoms (EPS): Barnes Akathisia Rating Scale (BARS) and Simpson-Angus Scale (SAS)
- Psychiatric status scales:
  - Schizophrenia or schizoaffective disorder: Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS)
  - Mood Disorder: Montgomery-Åsberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS)
- All outcomes were analyzed descriptively

RESULTS

Participants

- The overall LTE population included 430 participants (KINECT, n = 46; KINECT 3, n = 220; KINECT 4, n = 164)
- 71.7% of participants had a diagnosis of schizophrenia/schizoaffective disorder and 28.3% had a diagnosis of mood disorder
- Baseline demographics and disease characteristics in the LTE population were similar between pooled valbenazine treatment groups (Table 1)

Safety

- Mean changes in psychiatric scale scores from baseline to end of treatment (Week 48) and end of treatment-free follow-up (Week 52) indicated that symptoms remained stable in the diagnostic subgroups (Figure 2)
- The incidence of treatment-emergent AEs (TEAEs) in all participants was 66.5% and of discontinuations due to AEs was 14.7% (Table 2)
- The 3 most commonly reported TEAEs in the schizophrenia/schizoaffective disorder subgroup (n = 309) were urinary tract infection (6.1%), headache (5.8%), and somnolence (5.2%)
- The 3 most commonly reported TEAEs in the mood disorder subgroup (n = 121) were headache (12.4%), urinary tract infection (10.7%), and somnolence (9.1%)
A lifetime history of suicidal ideation or behavior was reported in 39.8% of all participants (Table 1).

Long-term valbenazine treatment did not appear to increase suicidality, based on spontaneous TEAE reporting or C-SSRS responses (Table 2).

**TABLE 1**

### Baseline Characteristics (Safety Population)\(^{a}\)

<table>
<thead>
<tr>
<th></th>
<th>VALBENAZINE 40 MG (N = 197)</th>
<th>VALBENAZINE 80 MG (N = 230)</th>
<th>ALL PARTICIPANTS (N = 427)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, years</td>
<td>56.2</td>
<td>56.9</td>
<td>56.6</td>
</tr>
<tr>
<td>&lt;65 years, %</td>
<td>81.7</td>
<td>81.3</td>
<td>81.5</td>
</tr>
<tr>
<td>Male, %</td>
<td>59.4</td>
<td>52.2</td>
<td>55.5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, %</td>
<td>56.3</td>
<td>65.7</td>
<td>61.4</td>
</tr>
<tr>
<td>Black, %</td>
<td>37.6</td>
<td>31.3</td>
<td>34.2</td>
</tr>
<tr>
<td>Body mass index</td>
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<td></td>
</tr>
<tr>
<td>Mean, kg/m(^2)</td>
<td>28.1</td>
<td>28.4</td>
<td>28.2</td>
</tr>
<tr>
<td>25 to &lt;30, %</td>
<td>33.5</td>
<td>35.7</td>
<td>34.7</td>
</tr>
<tr>
<td>≥30, %</td>
<td>36.5</td>
<td>35.7</td>
<td>36.1</td>
</tr>
<tr>
<td>Mean age at TD diagnosis, years</td>
<td>48.6</td>
<td>48.2</td>
<td>48.4</td>
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<tr>
<td>Psychiatric diagnosis and history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current schizophrenia/schizoaffective disorder, %</td>
<td>76.6</td>
<td>67.4</td>
<td>71.7</td>
</tr>
<tr>
<td>Current mood disorder, %</td>
<td>23.4</td>
<td>32.6</td>
<td>28.3</td>
</tr>
<tr>
<td>Lifetime history of suicidality, %(^{b})</td>
<td>39.1</td>
<td>40.4</td>
<td>39.8</td>
</tr>
<tr>
<td>Concomitant use of antipsychotics</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Any concomitant antipsychotic, %</td>
<td>88.3</td>
<td>83.0</td>
<td>85.5</td>
</tr>
<tr>
<td>Atypical only, %</td>
<td>71.6</td>
<td>68.3</td>
<td>69.8</td>
</tr>
<tr>
<td>Typical only or both, %</td>
<td>16.8</td>
<td>14.8</td>
<td>15.7</td>
</tr>
<tr>
<td>Psychiatric scales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS Total, mean(^{c})</td>
<td>57.2</td>
<td>49.8</td>
<td>53.5</td>
</tr>
<tr>
<td>PANSS Positive Symptoms, mean(^{c})</td>
<td>13.4</td>
<td>11.5</td>
<td>12.4</td>
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<tr>
<td>PANSS Negative Symptoms, mean(^{c})</td>
<td>15.4</td>
<td>13.5</td>
<td>14.5</td>
</tr>
<tr>
<td>PANSS General Psychopathology, mean(^{c})</td>
<td>28.4</td>
<td>24.8</td>
<td>26.6</td>
</tr>
<tr>
<td>CDSS total, mean(^{c})</td>
<td>2.4</td>
<td>1.9</td>
<td>2.1</td>
</tr>
<tr>
<td>MADRS total, mean(^{d})</td>
<td>6.2</td>
<td>5.5</td>
<td>5.7</td>
</tr>
<tr>
<td>YMRS total, mean(^{d})</td>
<td>2.6</td>
<td>2.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**Notes:**

\(^{a}\)At the time of this presentation, baseline data was not available for 3 participants.

\(^{b}\)Lifetime history of suicidality was defined as endorsement of any C-SSRS category for suicidal ideation (items 1–5) or suicidal behavior (items 6–10).

\(^{c}\)PANSS and CDSS were administered only to participants with schizophrenia/schizoaffective disorder (40 mg, n = 154; 80 mg, n = 155).

\(^{d}\)YMRS and MADRS were administered only to participants with mood disorder (40 mg, n = 46; 80 mg, n = 75).

**Abbreviations:** C-SSRS, Columbia-Suicide Severity Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; MADRS, Montgomery-Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; TD, tardive dyskinesia; YMRS, Young Mania Rating Scale.
**FIGURE 2**

**MEAN CHANGES IN PSYCHIATRIC SCALE SCORES AFTER LONG-TERM VALBENAZINE TREATMENT (WEEK 48) AND TREATMENT WASHOUT (WEEK 52)**

**A**  
**PANSS Total and Subscale Scores**

<table>
<thead>
<tr>
<th>Week 48</th>
<th>Week 52</th>
<th>Week 48</th>
<th>Week 52</th>
<th>Week 48</th>
<th>Week 52</th>
<th>Week 48</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS Total</td>
<td>-0.3</td>
<td>-1.3</td>
<td>-1.0</td>
<td>-0.5</td>
<td>0.4</td>
<td>-0.4</td>
<td>-0.9</td>
</tr>
<tr>
<td>PANSS Positive Symptoms</td>
<td>-0.8</td>
<td>-1.3</td>
<td>-0.2</td>
<td>-0.5</td>
<td>-0.1</td>
<td>-0.4</td>
<td>-0.9</td>
</tr>
<tr>
<td>PANSS Negative Symptoms</td>
<td>-0.6</td>
<td>-1.0</td>
<td>-0.3</td>
<td>-0.7</td>
<td>-0.1</td>
<td>-0.4</td>
<td>-0.9</td>
</tr>
<tr>
<td>PANSS General Psychopathology</td>
<td>-0.6</td>
<td>-1.0</td>
<td>-0.3</td>
<td>-0.7</td>
<td>-0.1</td>
<td>-0.4</td>
<td>-0.9</td>
</tr>
</tbody>
</table>

**B**  
**CDSS, MADRS, and YMRS Total Scores**

<table>
<thead>
<tr>
<th>Week 48</th>
<th>Week 52</th>
<th>Week 48</th>
<th>Week 52</th>
<th>Week 48</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDSS Total</td>
<td>-0.4</td>
<td>-0.4</td>
<td>-0.4</td>
<td>-0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>MADRS Total</td>
<td>-1.1</td>
<td>-1.1</td>
<td>-1.1</td>
<td>-1.1</td>
<td>0.4</td>
</tr>
<tr>
<td>YMRS Total</td>
<td>-1.2</td>
<td>-1.2</td>
<td>-1.2</td>
<td>-1.2</td>
<td>-1.0</td>
</tr>
</tbody>
</table>

**Notes:** PANSS and CDSS were administered only to participants with schizophrenia/schizoaffective disorder (40 mg, n = 154; 80 mg, n = 155). YMRS and MADRS were administered only to participants with mood disorder (40 mg, n = 46; 80 mg, n = 75).

**Abbreviations:** CDSS, Calgary Depression Scale for Schizophrenia; MADRS, Montgomery-Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean; YMRS, Young Mania Rating Scale.
### TABLE 2

**TREATMENT-EMERGENT ADVERSE EVENTS BY DIAGNOSTIC SUBGROUP**

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Schizophrenia/Schizoaffective Disorder</th>
<th>ALL PARTICIPANTS</th>
<th>Mood Disorder</th>
<th>ALL PARTICIPANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Valbenazine 40 mg (N = 154)</td>
<td>67 (39.3)</td>
<td>16 (10.6)</td>
<td>56 (74.7)</td>
</tr>
<tr>
<td></td>
<td>Valbenazine 80 mg (N = 155)</td>
<td>108 (69.7)</td>
<td>48 (15.5)</td>
<td>87 (71.9)</td>
</tr>
<tr>
<td></td>
<td>All participants (N = 309)</td>
<td>199 (64.4)</td>
<td>7 (15.2)</td>
<td>87 (71.9)</td>
</tr>
</tbody>
</table>

- Any TEAE, n (%) 91 (59.1) 108 (69.7) 199 (64.4) 31 (67.4) 56 (74.7) 87 (71.9)
- Discontinuation due to TEAE 25 (16.2) 23 (14.8) 48 (15.5) 7 (15.2) 8 (10.7) 15 (12.4)
- TEAE leading to dose reduction 6 (3.9) 10 (6.5) 16 (5.2) 4 (8.7) 9 (12.0) 13 (10.7)

**TEAEs by preferred term, %a**

- Headache 7 (4.5) 11 (7.1) 18 (5.8) 7 (15.2) 8 (10.7) 15 (12.4)
- Urinary tract infection 11 (7.1) 8 (5.2) 19 (6.1) 4 (8.7) 9 (12.0) 13 (10.7)
- Somnolence 10 (6.5) 6 (3.9) 16 (5.2) 5 (10.9) 6 (8.0) 11 (9.1)
- Fatigue 8 (5.2) 5 (3.2) 13 (4.2) 6 (13.0) 3 (4.0) 9 (7.4)
- Suicidal ideation 7 (4.5) 7 (4.5) 14 (4.5) 2 (4.3) 4 (5.3) 6 (5.0)
- Dizziness 4 (2.6) 7 (4.5) 11 (3.6) 2 (4.3) 5 (6.7) 7 (5.8)
- Diarrhea 3 (1.9) 6 (3.9) 9 (2.9) 3 (6.5) 5 (6.7) 8 (6.6)
- Constipation 5 (3.2) 5 (3.2) 10 (3.2) 2 (4.3) 4 (5.3) 6 (5.0)
- Anxiety 3 (1.9) 4 (2.6) 7 (2.3) 4 (8.7) 4 (5.3) 8 (6.6)
- Depression 5 (3.2) 4 (2.6) 9 (2.9) 5 (10.9) 1 (1.3) 6 (5.0)
- Vomiting 5 (3.2) 4 (2.6) 9 (2.9) 2 (4.3) 4 (5.3) 6 (5.0)
- Nausea 1 (0.6) 3 (1.9) 4 (1.3) 4 (8.7) 4 (5.3) 8 (6.6)
- Back pain 1 (0.6) 2 (1.3) 3 (1.0) 5 (10.9) 4 (5.3) 9 (7.4)
- Bronchitis 2 (1.3) 0 2 (0.6) 1 (2.2) 8 (10.7) 9 (7.4)
- Arthralgia 1 (0.6) 3 (1.9) 4 (1.3) 1 (2.2) 5 (6.7) 6 (5.0)

**Note:** Reported in ≥5% of total participants in either diagnostic subgroup.

**Abbreviation:** TEAE, treatment-emergent adverse event.
In the overall LTE population, laboratory parameters were similar across treatment groups; mean changes were generally minimal and not clinically significant.

Some participants experienced a small increase in prolactin levels, although approximately 20% of all participants had elevated prolactin at baseline.

No notable ECG changes occurred, including the 81% of participants who were taking concomitant medications with a known potential to prolong QT.

There was no evidence of treatment-emergent parkinsonism, akathisia, or other significant treatment-induced abnormal movements based on BARS and SAS scores.

Although approximately 85% of participants were receiving ≥1 concomitant antipsychotic medication, there was no clinical evidence of drug interaction toxicities.

CONCLUSIONS

Valbenazine was generally well tolerated in adults with TD who received up to 48 weeks of treatment; tolerability was similar in participants with schizophrenia and participants with mood disorders.

Mean score changes on the PANSS, CDSS, YMRS, and MADRS indicated that psychiatric status generally remained stable; valbenazine also had no notable effects on cardiac or hepatic function.

These analyses, along with the long-term effects of valbenazine on TD in participants with schizophrenia/schizoaffective disorder or mood disorder (see Posters P5-010 and P5-005, respectively) indicate that valbenazine may be an effective, long-term treatment for managing TD regardless of underlying psychiatric diagnosis.

DISCLOSURE

Writing and editorial assistance was provided by Prescott Medical Communications Group, Inc., Chicago, IL.

REFERENCES